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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,560	01/27/2006	Ian Alexander Shiels	36672.6	3534

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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,560	SHIELS ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 10-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 10-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-5 and 10-23 are pending.

Claim Objections

2. Claims 13 and 14 are objected to. For clarity, the phrase "wherein said compounds have chemical structures" should be inserted before "as follows". Alternatively, the claims could be constructed in a manner analogous to claim 21.

Claim Rejections - 35 USC § 112

3. Applicant's arguments, see pages 39-41, filed 10/16/2007, with respect to 35 U.S.C. 112, second paragraph, have been fully considered and are persuasive in light of the amendments to the claims. The rejection of claim 20 has been withdrawn.

4. Applicant's arguments, see pages 41-46, filed 10/16/2007, with respect to 35 U.S.C. 112, first paragraph, have been fully considered and are persuasive in light of the amendments to the claims. The rejection of claims 1, 2 and 6-20 has been withdrawn.

Claim Rejections - 35 USC § 102

5. Applicant's arguments, see pages 46-50, filed 10/16/2007, with respect to 35 U.S.C. 102(b) have been fully considered and are persuasive. The rejection of claims 1, 2 and 6-20 has been withdrawn.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

> having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Previously Issued Grounds for Rejection

7. Claims 1, 2 and 6-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woodruff *et al.* (*Arthritis & Rheumatism*, **2002**, *46*, 2476-85) in view of Fairlie (WO 99/00406) and Kivitz *et al.* (*J. Fam. Prac.*, **2002**, *51*, 530-7). Woodruff teach administering an effective amount of the elected species for the treatment of rheumatoid arthritis. Specifically, the compound is a peptidomimetic compound of formula 1 wherein A is NH-acyl, B is the side chain of L-Phenylalanine, C is the side chain of L- Proline, D is the side chain of D-cyclohexylalanine, E is the side chain of L-tryptophan, F is the side chain of L-arginine, and X is $-(CH_2)_nNH-$, where n is 3 ((AcF-[OPdChaWR]), abstract left column, paragraph 4, page 2477), satisfying the compound limitations in claims 1, 2, 6-9, 13, 14 and 16-23. Woodruff *et al.* also teach that the cyclic peptide AcF-[OPdChaWR] is a potent antagonist of human and rat C5a receptors on polymorphonuclear leukocytes (PMN's, left column, paragraph 4, page 2477), thus meeting the additional limitation of claim 10. Further Woodruff *et al.* teach a combination therapy of the cyclic peptide with ibuprofen, thus meeting the additional limitation of claim 15. Further, as evidenced by Fairlie, the cyclic analog of AcF-[OpdChaWR] has a C5aR affinity of 0.3 μM (Table 6, page 42), thus meeting the additional limitations of claims 11, and 12.

8. Woodruff *et al.* do not teach that AcF-[OpdChaWR] can be used to treat osteoarthritis. It would have been obvious to one of ordinary skill in the art to administer AcF-[OPdChaWR] to patients suffering from osteoarthritis. The skilled artisan would have been motivated to do so given the teaching of Kivitz *et al.* that pain and inflammation of rheumatoid arthritis and osteoarthritis patients can be treated with the same drugs, NSAIDs. There would have been a reasonable expectation of success given that Woodruff *et al.* teach that AcF-[OPdChaWR] can be used to treat inflammatory conditions (page 2477).

Applicant's Arguments in Traverse of the Rejection

9. Applicants traverse the rejection on the grounds that the Office has not established that the combined teachings of Woodruff, Fairlie and Kivitz would produce a predictable result with a reasonable expectation of success. In support of this position, Applicant submitted an independent, third-party Declaration under 37 C.F.R. §1.132 by Richard O. Day, Ph.D.

10. Dr. Day presents arguments illustrating the fundamental differences between osteoarthritis, the condition that is the subject of the instant claims, and rheumatoid arthritis, the condition that is the subject of the prior art.

> Osteoarthritis is a chronic degenerative disease affecting joints. For this reason osteoarthritis is also known as degenerative joint disease. In osteoarthritis the cartilage between the joints degenerates as the primary outcome of the pathophysiologic processes of osteoarthritis. Bone spurs, also known as osteophytes, are produced and fluid commonly accumulates in the joint spaces at the same time as the cartilage is destroyed. These pathological processes of formation of bone spurs, fluid accumulation in joints and cartilage degeneration and loss are associated with pain and often evidence of inflammation in the patient as the disease progresses. Inflammation is not the primary pathophysiologic process in osteoarthritis. The cartilage in joints may degenerate due to stress on the joint or injury to the joint but there are other factors that are important such as genetic constitution of the individual.
>
> Rheumatoid arthritis, in contrast to osteoarthritis, is a chronic autoimmune disease which manifests itself as inflammation of the synovial membrane lining the joints and this is

> known as synovitis. The inflammation causes joint swelling, pain and stiffness, the latter notably and in contrast to osteoarthritis, in the morning. The underlying cause of rheumatoid arthritis is not clearly understood but there are genetic factors involved and these are different from those relevant to osteoarthritis. A patient with rheumatoid arthritis may be prescribed a non-steroidal anti- inflammatory drug (NSAID) to treat the inflammation and associated pain. However NSAIDs do not halt the progression of rheumatoid arthritis. To tackle the underlying process of the disease causing synovitis and then damage to the joint anti-TNF agents have been employed to reduce joint inflammation in rheumatoid arthritic patients by blocking TNF. TNF is a protein that is an important driver of inflammation as a result of the body's normal immune response. But in the case of rheumatoid arthritis the TNF production continues and drives the synovitis and eventually damage to the joints.

11. To underscore the point that rheumatoid arthritis is a fundamentally different disease than osteoarthritis, Applicant submitted the reference Schwartzman, S., *et. al*. which discusses the efficacy of three TNF agents currently available in the United States of America to treat rheumatoid arthritis, infliximab, etanercept and adalimumab, none of which are indicated for osteoarthritis.

12. Dr. Day argues that given that the etiologies of rheumatoid arthritis and osteoarthritis are very different, osteoarthritis is a degenerative disease whereas rheumatoid arthritis is an autoimmune inflammatory disease, it is not possible to extrapolate from one disease to the other. In addressing the Kivitz paper, Dr. Day argues that "It is hardly surprising that an anti-inflammatory agent can be used to treat inflammation in two different disease states. There is much less inflammation in osteoarthritis and inflammation is a secondary process in osteoarthritis in comparison to rheumatoid arthritis. Also, NSAIDs are used successfully for their analgesic properties in osteoarthritis even when there is little evidence of inflammation present."

13. The cyclic peptides of the instant invention function as C5a receptor antagonist, a fact disclosed by Woodruff. The relationship between the C5a receptor antagonist and rheumatoid arthritis was established in the prior art. As a result, Dr. Day states: "Accordingly, it follows

that a C5a receptor antagonist would be expected to be useful in the treatment of rheumatoid arthritis." In order to motivate the use of a C5a receptor antagonist for the treatment of osteoarthritis, the role of this receptor in osteoarthritis would have to have been known in the prior art. Dr. Day states " I am not aware that such information was available prior to this application."

Examiner's Rebuttal

14. Applicants, through the support of the declaration of Dr. Day, have established the following: osteoarthritis and rheumatoid arthritis are fundamentally different diseases; the fact that NSAIDs can be used to manage symptoms of both diseases is insufficient grounds for employing a C5a receptor antagonist known to treat rheumatoid arthritis to treat osteoarthritis; and that the role of the C5a receptor in osteoarthritis was not known in the prior art. These arguments are persuasive and not contested.

15. Despite these arguments, the rejection of the claims is maintained on the grounds of an additional teaching in Woodruff (p. 2483, col. 2):

> The destruction of cartilage in osteoarthritis results from the IL-1-stimulated degradation of proteoglycans and inhibition of chondrocyte proteoglycan synthesis. NSAIDs protect the joint from swelling and cellular infiltration, but have little effect on disease progression, while glucocorticoids normalize proteoglycan synthesis. The NSAID ibuprofen diminishes the responses in the rat as measured by joint swelling and disturbance of gait, and these findings equate well with the response to most NSAIDs in the clinic. Ibuprofen is less successful in reducing the structural pathology in the rat joint, and this is also similar to human clinical findings. In contrast, the C5a receptor antagonist used in this study significantly reduces the degree of structural pathology in the joint as well as other signs of the disease in the rats. This ability to moderate structural changes in the joint is a clear advantage over most of the NSAIDs.

In this passage, Woodruff addresses the limitations of NSAID and ibuprofen therapy for osteoarthritis, which as Applicant notes only treats the symptoms of the condition but not

necessarily the underlying cause. Woodruff goes on to suggest that the cyclic peptide C5a receptor antagonist has additional effects over NSAIDs that are relevant to osteoarthritis. The fact that AcF-[OpdChaWR] "moderates structural changes in the joint" is reason to apply the compound to osteoarthritis even in the absence of information regarding the role of the C5a receptor in the disease. Given this teaching, the skilled artisan would have been motivated to use AcF-[OpdChaWR] taught by Woodruff to treat osteoarthritis.

16. Claims 1-5 and 10-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woodruff *et al.* (*Arthritis & Rheumatism*, **2002**, *46*, 2476-85) and Fairlie (WO 99/00406), as applied to claim 1, 2 and 6-23 above, in further view of Woodruff *et al.* (U.S. Patent No. 7,410,945). Woodruff *et al.* teach the C5a receptor agonist AcF-[OpdChaWR] as well as the full genus of compounds recited in instant claim 1. It would have been obvious to use AcF-[OpdChaWR] as well as the full genus of cyclic peptide C5a receptor agonists to treat osteoarthritis for the reasons presented above which for the sake of brevity will not be repeated here. U.S. Patent No. 7,410,945 shares a common inventor with the instant application and is the basis for a nonstatutory double patenting rejection below. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR

1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 1, 2 and 6-23 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 7,410,945 in view of Woodruff *et al.* (*Arthritis & Rheumatism*, **2002**, *46*, 2476-85) and Fairlie (WO 99/00406). Claims 1-9 of U.S. Patent No. 7,410,945 recite the cyclic peptide C5a receptor antagonist AcPhe[Orn-Pro-D-Cyclohexylalanine-Trp-Arg] (also referred to as AcF-[OpdChaWR]) which is

identical to the elected species and to the active agent taught in Woodruff *et al.* It would have been obvious to use AcF-[OpdChaWR] to treat osteoarthritis for the reasons presented above which for the sake of brevity will not be repeated here.

19. Claims 1, 2 and 6-23 are likewise provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the following claims in view of Woodruff *et al.* (*Arthritis & Rheumatism*, **2002**, *46*, 2476-85) and Fairlie (WO 99/00406):

- claims 33-49 of copending Application No. 12/193,943, which recite the full genus of cyclic peptide C5a receptor antagonists encompassed by the elected species AcF-[OpdChaWR]) and recited in instant claim 1;
- claims 1-23 of copending Application No. 12/144,266, which recite the full genus of cyclic peptide C5a receptor antagonists encompassed by the elected species AcF-[OpdChaWR]) and recited in instant claim 1;
- claims 1-54 of copending Application No. 12/045,088, which recite the full genus of cyclic peptide C5a receptor antagonists encompassed by the elected species AcF-[OpdChaWR]) and recited in instant claim 1;
- claims 1-6, 8-10, 12 and 19-21 of copending Application No. 10/493,117, which recite the full genus of cyclic peptide C5a receptor antagonists encompassed by the elected species AcF-[OpdChaWR]) and recited in instant claim 1;
- claims 1-28 of copending Application No. 10/531,565, which recite the full genus of cyclic peptide C5a receptor antagonists encompassed by the elected species AcF-[OpdChaWR]) and recited in instant claim 1;

- claims 1-13 of copending Application No. 11/807,651, which recite the full genus of cyclic peptide C5a receptor antagonists encompassed by the elected species AcF-[OpdChaWR]) and recited in instant claim 1;
- claims 1-28 of copending Application No. 11/736,517, which recite the full genus of cyclic peptide C5a receptor antagonists encompassed by the elected species AcF-[OpdChaWR]) and recited in instant claim 1;

20. It would have been obvious to use AcF-[OpdChaWR] to treat osteoarthritis for the reasons presented above which for the sake of brevity will not be repeated here. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

21. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

22. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 9:00 A.M. to 3:00 P.M.

24. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

25. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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